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(71) Applicant
Merck & Co Inc

(Incorporated in the USA - New Jersey)

P O Box 2000, Rahway, New Jersey 07065-0900, United States of America

(72) Inventors
William C Campbell
Jeffrey N Clark

(74) Agent and/or Address for Service
A Hesketh
Merck & Co Inc European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, United Kingdom

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(54) Synergistic antiparasitic combinations of avermectin and pyrantel

(57) Synergistic combinations of avermectins and pyrantel or pyrantel pamoate, suitably in a ratio of 1:1-5000 are effective against human and animal parasites. Ivermectin is the preferred avermectin.

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TITLE OF THE INVENTION

NOVEL SYNERGISTIC ANTIPARASITIC COMBINATIONS

BACKGROUND OF THE INVENTION

Avermectin compounds are a series of natural products isolated from the fermentation broth of a strain of Streptomyces avermitilis. The series consists of eight compounds, four major and four minor. The compounds are disclosed in U.S. Patent 4,310,519. Certain derivatives of such compounds are also disclosed, such as the 22,23-dihydro derivatives described in U.S. Patent 4,199,569. The 13-deoxy derivatives of avermectin compounds are disclosed in U.S. Patents 4,171,314 and 4,173,571. The 4"-phosphate derivatives of the avermectin compounds with a 13-O-disaccharide group present, are disclosed in U.S. Patent 4,469,682.

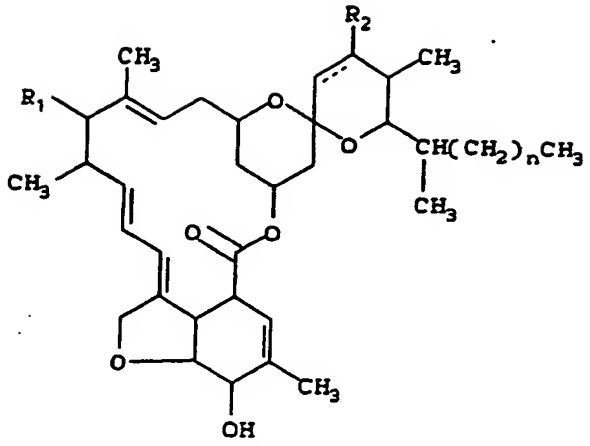
The synergistic combinations also include pyrantel or pyrantel pamoate which is disclosed in U.S. Patent 3,502,661. In addition, the 4"-amino and alkylated amino compounds are disclosed in U.S. Patent 4,427,663.

SUMMARY OF THE INVENTION

The instant disclosure describes certain synergistic combinations of avermectin compounds and pyrantel or pyrantel pamoate. Thus, it is an object of this invention to describe such synergistic combinations. It is a further object to describe the individual components of such synergistic combinations and the relative proportion of each component in the combination. A still further object of this invention is to describe the antiparasitic effects of such combinations. Further objects will become apparent from a reading of the following description.

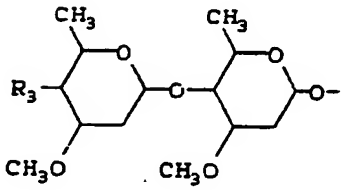
DESCRIPTION OF THE INVENTION

The instant invention consists of a combination of avermectin compounds and pyrantel or pyrantel pamoate which has a synergistic effect when administered to animals including humans for the treatment of parasitic diseases. The avermectin compounds of this invention have the following formula:



wherein n is 0 or 1;

R_1 is hydrogen, or

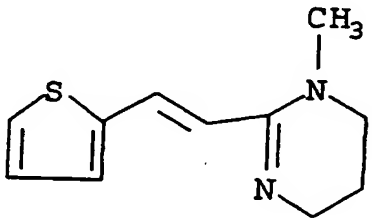


wherein R_3 is hydroxy, amino or C_{1-6} lower alkylamino and the 4"-phosphate derivative thereof when R_3 is hydroxy;

R_2 is hydrogen or hydroxy; and

the broken line indicates a single or a double bond; however, R_2 is present only when the broken line indicates a single bond.

The pyrantel compound that consitutes the second part of the instant synergistic combinations has the following structure:



and the pamoic acid salt ($C_{23}H_{16}O_6$) thereof which is disclosed in U.S. Patent 3,502,661.

When used as antiparasitic agents, the avermectin compounds are administered at dosage rates of from 0.001 to 10 mg of the active compound per kg of weight of the host animal. When used as an antiparasitic agent, the pyrantel or pyrantel pamoate is administered at dosage rates of from 1 to 20 mg of the active compound per kg of weight of the host animal.

The synergistic effects of the combination of the avermectin compounds with pyrantel or pyrantel pamoate is observed in providing for a reduced dosage of one or both of the components. Thus, a lessened quantity of the antiparasitic compounds is administered than normally would be required which results in a lessening of possible side effects and a lessening in the development of resistance. In

addition, there is observed the synergistic expansion of the spectrum of parasitic infections which may be successfully combatted than would be expected for a consideration of the spectra of activity of the individual components. Thus, the possibility of eliminating parasitic infections against which the individual components are ineffective or only partially effective is realized in the instant synergistic combination.

The parasitic infections against which the instant synergistic combination is particularly effecive are gastrointestinal worms found in mammals and avian species such as humans, dogs, cats, sheep, cattle, horses, pigs, chickens and other animals.

The parasitic infections against which the instant synergistic combination is particularly effective are species of the genera Ancylostoma, Strongyloides, Haemonchus, Arthropods, Toxocara, Toxascaris, Heterakis, Parascaris, Ascaris, Neoascaris, Ascarida, Dirofilaria, Arachnids, and the like.

In using the instant synergistic combination, the individual components are used in proportions which may extend to from 1 part of the avermectin compound to 1 part of pyrantel or pyrantel pamoate to from 1 part of the avermectin compound to 5000 parts of pyrantel or pyrantel pamoate.

The synergistic combination may be administered orally in unit dosage form such as a capsule, bolus, swallow tablet or chewable tablet, or as a liquid drench where used as an antiparasitic in mammals. The drench is normally a solution,

suspension or dispersion of the active ingredients usually in water together with a suspending agent such as bentonite and a wetting agent or like excipient. Generally, the drenches also contain an antifoaming agent. Drench formulations generally contain from about 0.001 to 0.5% by weight of the active compounds. Preferred drench formulations may contain from 0.01 to 1% by weight. The capsules and boluses comprise the active ingredients admixed with a carrier vehicle such as starch, talc, magnesium stearate, or dicalcium phosphate.

Where it is desired to administer the synergistic combination in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compounds usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredients with suitable finely divided diluents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the synergistic combination is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the antiparasitic

combination of our invention may be administered to animals parenterally, for example, by intraruminal, intramuscular, intratracheal, or subcutaneous injection in which event the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral vehicles such as organic preparations using solketal, glycerol, formal and aqueous parenteral formulations are also used. The active compounds are dissolved or suspended in the parenteral formulation for administrations; such formulations generally contain from 0.005 to 5% by weight of the active compound.

Specific formulations containing avermectin compounds and pyrantel or pyrantel pamoate which have synergistic antiparasitic effects are as follows:

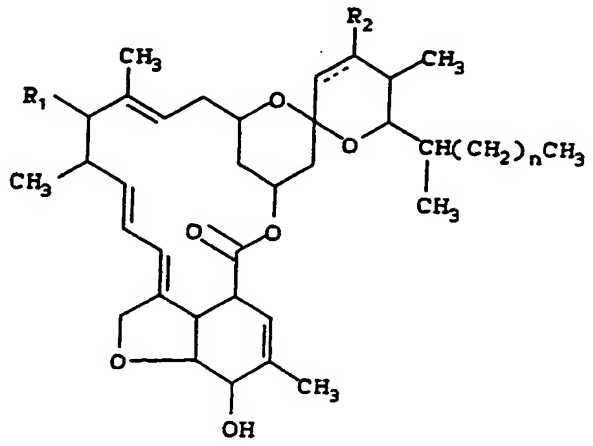
A bolus is made, consisting of 2.5 g starch, 2.5 g lactose, 100 mg pyrantel pamoate and 10 mg ivermectin. The bolus is administered, by means of a balling gun, to a calf weighing 100 kg body weight and harboring parasites of the genera Haemonchus, Trichostrongylus, Ostertagia, Parafilaria, Damalinia, Bunostomum, Neoascaris, Amblyomma, Linognathus and Sarcoptes. The treatment results in a high degree of efficacy against the said parasite species.

In addition, an oral drench, or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver the avermectin at 0.2 mg/kg and pyrantel pamoate at 1.0 mg/kg.

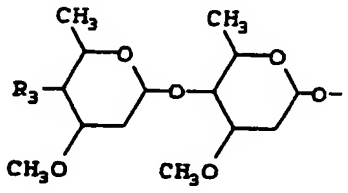
A solution or suspension or other formulation suitable for parenteral administration may be prepared containing the active ingredients in quantities sufficient to provide avermectin at a dosage of 0.2 mg/kg and pyrantel pamoate at 1.0 mg/kg.

WHAT IS CLAIMED IS:

1. An antiparasitic synergistic combination of an avermectin compound having the formula:



wherein n is 0 or 1;
R_1 is hydrogen,



wherein R_3 is hydroxy, amino or C_{1-6} lower alkyl amino and the 4"-phosphate derivative thereof when R_3 is hydroxy;

R_2 is hydrogen or hydroxy; and

the broken line indicates a single or a double bond; however, R_2 is present only when the broken line indicates a single bond;

and pyrantel or pyrantel pamoate.

2. The synergistic combination of Claim 1 wherein compounds are present at a proportion of from 1 part of the avermectin compound to 1 part of pyrantel or pyrantel pamoate, to from 1 part of the avermectin compound to 5000 parts of pyrantel or pyrantel pamoate.

3. An antiparasitic formulation comprising an inert carrier and from 0.001 to 5% by weight of the synergistic combination of Claim 1.

4. The use of the synergistic combination of Claim 1 for the preparation of a medicament useful for the treatment of parasitic infections.

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